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Proposed Re-evaluation Decision

Streptomycin

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Overview

What Is the Proposed Re-evaluation Decision?

After a re-evaluation of streptomycin, Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing continued registration of the product containing streptomycin for sale and use in Canada.

An evaluation of available scientific information found that products containing streptomycin do not present unacceptable risks to human health or the environment when used according to label directions. As a condition of the continued registration of streptomycin uses, new risk-reduction measures must be included on the labels of all products. No additional data are being requested at this time.

This proposal affects all end-use products containing streptomycin registered in Canada. Once the final re-evaluation decision is made, the registrants will be instructed on how to address any new requirements.

This Proposed Re-evaluation Decision is a consultation document[1] that summarizes the science evaluation for streptomycin and presents the reasons for the proposed re-evaluation decision. It also proposes additional risk-reduction measures to further protect human health and the environment.

The information is presented in two parts. The Overview describes the regulatory process and key points of the evaluation, while the Science Evaluation provides detailed technical information on the assessment of streptomycin.

The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document. Please forward all comments to Publications (please see contact information on the cover page of this document).

What Does Health Canada Consider When Making a Re-evaluation Decision?

The PMRA's pesticide re-evaluation program considers potential risks, as well as value, of pesticide products to ensure they meet modern standards established to protect human health and the environment. Regulatory Directive DIR2001-03, *PMRA Re-evaluation Program*, presents the details of the re-evaluation activities and program structure.

Streptomycin, one of the active ingredients in the current re-evaluation cycle, has been re-evaluated under Re-evaluation Program 1. This program relies as much as possible on foreign reviews, typically United States Environmental Protection Agency (USEPA) Reregistration

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[1] "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

Eligibility Decision (RED) documents. For products to be re-evaluated under Program 1, the foreign review must meet the following conditions:

- it covers the main science areas, such as human health and the environment, that are necessary for Canadian re-evaluation decisions;
- it addresses the active ingredient and the main formulation types registered in Canada; and
- it is relevant to registered Canadian uses.

Given the outcome of foreign reviews and a review of the chemistry of Canadian products, the PMRA will propose a re-evaluation decision and appropriate risk-reduction measures for Canadian uses of an active ingredient. In this decision, the PMRA takes into account the Canadian use pattern and issues (e.g. the federal Toxic Substances Management Policy [TSMP]).

Based on the health and environmental risk assessments published in a 1992 RED and a 2006 Tolerance Reassessment Eligibility Decision (TRED), the USEPA concluded that streptomycin was eligible for reregistration provided risk-reduction measures were adopted. The PMRA compared the American and Canadian use patterns and found the USEPA assessments described in the RED and TRED were an adequate basis for the proposed Canadian re-evaluation decision.

For more details on the information presented in this overview, please refer to the Science Evaluation in this consultation document.

What Is Streptomycin?

Streptomycin is a bactericide used to control fire blight on apples and pears. It is applied using ground application equipment when trees are at 20 to 30% bloom and again during blossom time.

Health Considerations

Can Approved Uses of Streptomycin Affect Human Health?

Streptomycin is unlikely to affect your health when used according to the revised label directions.

People could be exposed to streptomycin by consuming food and water, working as a mixer/loader/applicator or by entering treated sites. The PMRA considers two key factors when assessing health risks: the levels at which no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (e.g. children and nursing mothers). Only uses for which exposure is well below levels that cause no effects in animal testing are considered acceptable for continued registration.

The USEPA concluded that streptomycin was unlikely to affect human health. These conclusions apply to the Canadian situation.

Maximum Residue Limits

The *Food and Drugs Act* prohibits the sale of food containing a pesticide residue that exceeds the established maximum residue limit (MRL). Pesticide MRLs are established for *Food and Drugs Act* purposes through the evaluation of scientific data under the *Pest Control Products Act*. Each MRL value defines the maximum concentration in parts per million (ppm) of a pesticide allowed in or on certain foods. Food containing a pesticide residue that does not exceed the established MRL does not pose an unacceptable health risk.

Streptomycin is currently registered in Canada for use on apples and pears and could be used in other countries on crops that are imported into Canada. No specific MRLs have been established for streptomycin in Canada. Where no specific MRL has been established, a default MRL of 0.1 ppm applies, which means that pesticide residues in a food commodity must not exceed 0.1 ppm. However, changes to this general MRL may be implemented in the future, as indicated in Discussion Document DIS2006-01, *Revocation of 0.1 ppm as a General Maximum Residue Limit for Food Pesticide Residues [Regulation B.15.002(1)]*. If and when the general MRL is revoked, a transition strategy will be established to allow permanent MRLs to be set.

Environmental Considerations

What Happens When Streptomycin Is Introduced Into the Environment?

Streptomycin is unlikely to affect non-target organisms when used according to the revised label directions.

The USEPA concluded that the reregistration of streptomycin was acceptable. These conclusions apply to the Canadian situation.

Measures to Minimize Risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

- **Human Health**

A statement to address the antibiotic resistance concern is required.

- **Environment**

Environmental hazard statements are required.

Next Steps

Before making a final re-evaluation decision on streptomycin, the PMRA will consider all comments received from the public in response to this consultation document. The PMRA will then publish a Re-evaluation Decision[2] document that will include the decision, the reasons for it, a summary of comments received on the proposed decision and the PMRA's response to these comments.

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2 "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*.

Science Evaluation

1.0 Introduction

Streptomycin is a bactericide that acts by inhibiting protein synthesis.

Following the re-evaluation announcement for streptomycin, the registrant of the end-use product in Canada indicated its intention to provide continued support for all uses included on the label of the commercial product in Canada.

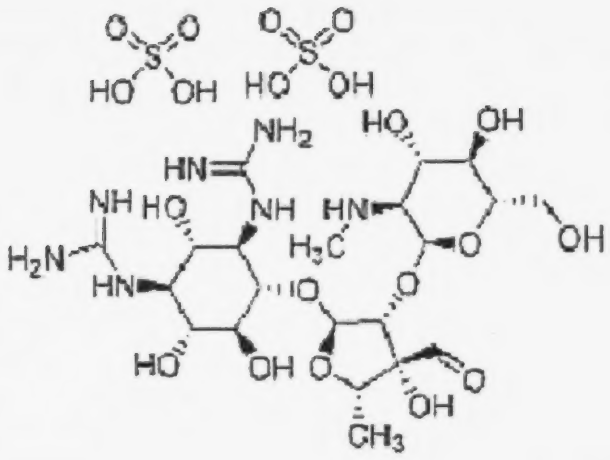
The PMRA used assessments of streptomycin from the United States Environmental Protection Agency (USEPA). The USEPA Reregistration Eligibility Decision (RED) for streptomycin, dated September 1992, and the USEPA Tolerance Reassessment Eligibility Decision (TRED), dated June 2006, as well as other information on the regulatory status of streptomycin in the United States can be found on the USEPA Pesticide Registration Status page at www.epa.gov/pesticides/reregistration/status.htm.

2.0 The Technical Grade Active Ingredient, Its Properties and Uses

2.1 Identity of the Technical Grade Active Ingredient

Common name		Streptomycin sulfate
Function		Antibiotic
Chemical family		Aminogycoside antibiotic isolated from the bacterium *Streptomyces griseus*
Chemical name		O-2-deoxy-2-(methylamino)-α-L-glucopyranosyl-(1→2)-O-5-deoxy-3-C-formyl-α-L-lyxofuranosyl-(1→4)-N,N'-bis(aminoiminomethyl)-D-streptamine
1	**International Union of Pure and Applied Chemistry (IUPAC)**	1,1-{1-L-(1,3,5/2,4,6)-4-[5-deoxy-2-O-(2-deoxy-2-methylamino-α-L-glucopyranosyl)-3-C-formyl-α-L-lyxofuranosyloxy]-2,5,6-trihydroxycyclohex-1,3-ylene}diguanidine
2	**Chemistry Abstracts Service (CAS)**	O-2-deoxy-2-(methylamino)-α-L-glucopyranosyl-(1→2)-O-5-deoxy-3-C-formyl-α-L-lyxofuranosyl-(1→4)-N,N'-bis(aminoiminomethyl)-D-streptamine
CAS Registry Number		57-92-1 and 3810-74-0 (streptomycin)
Molecular formula		$(C_{21}H_{39}N_7O_{12})_2 \cdot 3H_2SO_4$

Structural formula



Molecular weight 1467.48

2.2 Comparison of Use Patterns in Canada and the United States

Streptomycin is an antibiotic registered in Canada for the control of fire blight on apples and pears. It is applied when trees are at 20 to 30% bloom and again during blossom time. Streptomycin is applied at a maximum concentration of 100 ppm (144 g a.i./1000 L water). The maximum number of applications recommended on the label is three per season and the maximum amount recommended on the label is 1294 g a.i. per hectare per season. The end-use product is formulated as a wettable powder and applied by ground only.

The American and Canadian use patterns were compared. The registered formulation type, use sites and maximum application rate for streptomycin in Canada are also part of the American streptomycin use pattern. Therefore, the assessments conducted in the USEPA RED and TRED are an adequate basis for the re-evaluation of uses of streptomycin in Canada.

All current uses are being supported by the registrant and were therefore considered in the re-evaluation of streptomycin. Appendix I lists the streptomycin product that is registered as of 20 February 2008 under the authority of the *Pest Control Products Act*.

3.0 Impact on Human Health and the Environment

In its 1992 RED, the USEPA concluded that the use of products containing streptomycin registered at the time of the RED publication would not pose unreasonable risks or adverse effects to humans or the environment and, therefore, are eligible for reregistration. After the RED, the USEPA published a TRED in 2006 that included an aggregate risk assessment that met the *Food Quality Protection Act* requirements.

3.1 Human Health

Toxicology studies in laboratory animals describe potential health effects resulting from various levels of exposure to a chemical and identify dose levels at which no effects are observed. Unless there is evidence to the contrary, it is assumed that effects observed in animals are relevant to humans and that humans are more sensitive to effects of a chemical than the most sensitive animal species.

In Canada, exposure to streptomycin may occur through consumption of food and water, while working as a mixer/loader/applicator or by entering treated sites. When assessing health risks, the PMRA considers two key factors: the levels at which no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (e.g. children and nursing mothers).

3.1.1 Occupational Exposure and Risk Assessment

Occupational risk is estimated by comparing potential exposures with the most relevant endpoint from toxicology studies being used to calculate a margin of exposure (MOE). This is compared to a target MOE incorporating safety factors protective of the most sensitive segment of the population. If the calculated MOE is less than the target MOE, it does not necessarily mean that exposure will result in adverse effects, but mitigation measures to reduce risk would be required.

Workers can be exposed to streptomycin when mixing, loading or applying the pesticide and when entering a treated site to conduct activities such as scouting or handling of treated crops.

The USEPA did not conduct a quantitative risk assessment from dermal exposure because only minimal dermal absorption was expected. Oral absorption of chemicals related to streptomycin is less than 1% because of the charged nature of the molecules. The skin has a protective barrier role in comparison to the lining of the gastrointestinal tract, and dermal absorption is expected to be much less than by the oral route. Although a dermal exposure study was not available for streptomycin, dermal absorption at environmental concentrations was expected to be so low that toxicity by the dermal route was not of concern.

Although inhalation exposure of workers was not quantified by the USEPA, it is not expected to be of concern based on the USEPA's assessment of residential handlers. Inhalation exposure was assessed for homeowners applying streptomycin to fruit trees and shrubs using a low pressure handwand. The resulting MOE was 75 000, which was well below the USEPA's level of concern (target MOE = 100).

Streptomycin is reported to have caused various allergic reactions in humans, including skin rashes, itchy sensations, nausea and headaches. The restricted-entry interval on the current Canadian label is 24 hours. The Canadian label also requires workers to wear chemical-resistant coveralls over a long-sleeved shirt and long pants, chemical-resistant gloves, socks and chemical-resistant footwear during mixing, loading, application, clean-up and repair. In addition, chemical-resistant headgear must be worn during application for overhead exposure except when

handlers are in an enclosed cab. This equipment is considered adequate to mitigate the potential for allergic reactions in workers. No additional mitigation measures are required.

3.1.2 Exposure From Food and Drinking Water

No acute endpoints of concern were identified by the USEPA. On this basis, acute risk assessments were not conducted.

Chronic dietary risk is estimated by determining how much of a pesticide residue may be ingested with the daily diet and comparing this potential exposure to an acceptable daily intake, which is the dose at which an individual could be exposed over the course of a lifetime and expect no adverse health effects. The acceptable daily intake is referred to as the ADI in Canada, and, in the RED, it is expressed as the chronic population adjusted dose (cPAD). The ADI is based on a relevant endpoint from toxicology studies and on safety factors protective of the most sensitive subpopulation.

The USEPA conducted an assessment of dietary risk from chronic exposure to food only. It was assumed that 20% of apples and 30% of pears were treated with streptomycin in the United States and that residues were at 0.25 ppm, which is equal to the established tolerance level. The highest dietary exposure was found to be 0.002 mg/kg bw/day for children 1 to 2 years old, which represented 4.8% of the cPAD.

Screening level surface water and groundwater estimates were calculated using Tier I estimate drinking water concentrations (EDWCs). Unrefined annual averages were 51.4 ppb and 1.2 ppb for surface and ground water, respectively. These estimates were based on an aerial application scenario at the maximum application rate of 772 g a.i./ha.

3.1.3 Aggregate Risk Assessment

Aggregate risk combines the different routes of exposure to streptomycin (i.e. from food, water and residential exposure).

No acute endpoints of concern were identified by the USEPA. On this basis, acute risk assessments were not conducted. The chronic aggregate risk assessment of streptomycin was based on high-end exposures and conservative endpoints.

In its TRED, the USEPA estimated that the highest exposure to streptomycin from food and drinking water was 4.5×10^{-3} mg/kg bw/day for infants, which utilized 9.0% of the cPAD. The USEPA considered the estimated exposure to streptomycin from food and drinking water to be below the level of concern and no additional mitigation measures with respect to dietary risk were required.

Although chronic exposure from uses of streptomycin in residential settings is unlikely, as a worst-case scenario, the USEPA aggregated the residential inhalation exposure with the dietary exposure to streptomycin from food and drinking water for adults, and found that it represented 4% of the cPAD. The combined inhalation and dietary exposure was below the level of concern.

The USEPA concluded that combined residues of streptomycin from food, drinking water and residential exposures would not result in an aggregate risk of concern to any population group.

Patients being treated with streptomycin injections may also consume food containing streptomycin residues. However, the dose for injection is considered to be equivalent to an oral dose of 1500 mg/kg bw/day, while dietary exposure was estimated at 0.002 mg/kg bw/day. The dietary exposure from pesticidal uses of streptomycin was negligible compared to drug exposure and would not contribute to drug toxicity. The USEPA concluded that there were no concerns for dietary contribution of streptomycin exposure to patients receiving streptomycin through drug injection.

The American assessments were based on a conservative Tier I assessment of exposure from food, using tolerance levels and the assumption that 20% of apples and 30% of pears were treated. The estimated percentage crop treated with streptomycin in Canada is less than the estimates in the United States. Canadian potential aggregate exposure scenarios were adequately addressed by the USEPA aggregate risk assessment and the USEPA conclusions are considered applicable to Canadian uses of streptomycin.

3.1.4 Cumulative Effects

The USEPA has not determined whether streptomycin has a common mechanism of toxicity with other substances or whether it shares a toxic metabolite produced by other substances. Therefore, it was assumed that streptomycin does not share a common mechanism of toxicity with other substances and a cumulative risk assessment was not required.

3.1.5 Antibiotic Resistance

Streptomycin has been used for more than 60 years as a human drug, and bacterial resistance to streptomycin has long been recognized.

Streptomycin as a drug is usually given by injection at the dose of 15 mg/kg bw/day. This was estimated to be 3000 to 12,000 times greater than the potential residue in food resulting from pesticidal uses. The USEPA concluded that antibiotic resistance is unlikely to result from food exposure because the anticipated dietary residues are so low. If bacterial resistance to streptomycin from the pesticidal use of streptomycin were to occur, it would be from the development of resistance from non-pathogenic bacteria in orchards, which later transfer their resistance to human bacterial pathogens. The USEPA indicated that it may consider antibiotic resistance in future actions such as registration renewal or approval of new uses. The USEPA requested the addition of statements to the label to ensure judicious use of streptomycin.

The PMRA requires an additional label statement to ensure that the product is used only when absolutely necessary (see Appendix III, Label Amendments for the Product Containing Streptomycin).

3.2 Environment

3.2.1 Environmental Risk Assessment

Based on a hazard assessment, the USEPA concluded the following:

- An acute avian oral toxicity study on bobwhite quail showed that streptomycin had an lethal dose to 50% (LD_{50}) greater than or equal to 2000 mg/kg. This indicated that streptomycin is practically non-toxic to upland bird species on an acute oral basis. In two subacute avian dietary studies, the lethal concentration to 50% (LC_{50}) was greater than or equal to 5620 and 4640 ppm, respectively, for bobwhite quail and mallard duck. These indicated that streptomycin is practically non-toxic to birds on a dietary and acute oral basis.

- An acute honey bee study indicated that streptomycin is practically non-toxic to honey bees, and the potential for streptomycin to have adverse effects on pollinators and other beneficial insects was expected to be low.

- Two 96-hour freshwater fish toxicity studies on rainbow trout and bluegill showed the LC_{50} was greater than or equal to 180 ppm for both studies. These data indicated that streptomycin is slightly toxic to both cold- and warm-water fish species. A supplemental study suggested that streptomycin was practically non-toxic to freshwater invertebrates.

- The effect concentration to 50% (EC_{50}) was determined to be 0.86 mg/L for the most sensitive species of algae. This indicated that streptomycin is toxic to algae.

Conclusions derived by the USEPA in the RED are considered relevant to the Canadian situation. The following environmental hazard statement is required to be added to the end-use product: "This product is toxic to algae. DO NOT apply this product directly to freshwater habitats (such as lakes, rivers, sloughs, ponds, prairie potholes, creeks, marshes, streams, reservoirs and wetlands), estuarine/marine habitats. DO NOT contaminate irrigation or drinking water supplies or aquatic habitats by cleaning of equipment or disposal of wastes."

3.2.2 Toxic Substances Management Policy Considerations

The management of toxic substances is guided by the 1995 federal Toxic Substances Management Policy, which puts forward a preventive and precautionary approach to deal with substances that enter the environment and could harm the environment or human health. The policy provides decision makers with direction and sets out a science-based management framework to ensure that federal programs are consistent with its objectives. One of the key management objectives is virtual elimination from the environment of toxic substances that result predominantly from human activity and that are persistent and bioaccumulative. These substances are referred to in the policy as Track 1 substances.

The federal Toxic Substances Management Policy and PMRA Regulatory Directive DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*, were taken into account during the re-evaluation of streptomycin. The PMRA has reached the following conclusions.

The *n*-octanol–water partition coefficient (log K_{ow}) of streptomycin was waived by the USEPA. Streptomycin is moderately persistent in aerobic soil. The aerobic soil half-life is 25 days, which is below the TSMP Track 1 criterion of 180 days. Streptomycin is a naturally occurring antibiotic, which precludes it from being classified as a candidate for virtual elimination.

4.0 Proposed Re-evaluation Decision

The PMRA has determined that streptomycin is acceptable for continued registration with the implementation of the proposed risk-reduction measures. These measures are required to further protect human health and the environment. The label of Canadian end-use product must be amended to include the label statements listed in Appendix III. A submission to implement label revisions will be required within 90 days of finalization of the re-evaluation decision.

5.0 Supporting Documentation

PMRA documents, such as Regulatory Directive DIR2001-03, and DACO tables can be found on our website at www.pmra-arla.gc.ca. PMRA documents are also available through the Pest Management Information Service. Phone: 1-800-267-6315 within Canada or 1-613-736-3799 outside Canada (long distance charges apply); fax: 613-736-3798; e-mail: pmra_infoserv@hc-sc.gc.ca.

The federal TSMP is available through Environment Canada's website at www.ec.gc.ca/toxics.

The USEPA RED document for streptomycin is available on the USEPA Pesticide Registration Status page at www.epa.gov/pesticides/reregistration/status.htm.

List of Abbreviations

a.i.	active ingredient
bw	body weight
cPAD	chronic population adjusted dose
EC_{50}	effect concentration 50%
FQPA	*Food Quality Protection Act*
g	gram(s)
ha	hectare(s)
kg	kilogram(s)
K_{ow}	*n*-octanol–water partition coefficient
L	litre(s)
LC_{50}	lethal concentration to 50%
LD_{50}	lethal dose to 50%
LOAEL	lowest observed adverse effect level
mg	milligram(s)
MOE	margin of exposure
MRL	maximum residue limit
N/A	not applicables
NOAEL	no observed adverse effect level
PCPA	*Pest Control Products Act*
ppb	parts per billion
ppm	parts per million
PRVD	Proposed Re-evaluation Decision
RED	Reregistration Eligibility Decision
RfD	reference dose
SF	safety factor
TSMP	Toxic Substances Management Policy
TRED	Tolerance Reassessment Eligibility Decision
UF	uncertainty factor
USEPA	United States Environmental Protection Agency

Appendix I Registered Products Containing Streptomycin as of 20 February 2008

Registration Number	Marketing Class	Registrant	Product Name	Formulation Type	Guarantee (%)
10305	Commercial	United Agri Products Canada Inc.	Streptomycin 17	Wettable powder	Streptomycin sulfate 25.2% (equivalent to 17% streptomycin)

Appendix II Toxicological Endpoints Used by the USEPA for Streptomycin Health Risk Assessments

Exposure Scenario (route and period of exposure)	Dose (mg/kg bw/day)	Study	Target UF/SF or MOE[a]
Acute dietary	N/A—Toxicity from acute dietary exposure not identified		
Chronic dietary (all populations)	NOAEL = 5 mg/kg bw/day Chronic RfD = 0.05 mg/kg bw/day	2-year feeding study in rats LOAEL = 10 mg/kg bw/day based on reduced body weight gain	UF = 100 FQPA SF = 1×
Inhalation exposure (all durations)	NOAEL = 5 mg/kg bw/day	2-year feeding study in rats LOAEL = 10 mg/kg bw/day based on reduced body weight gain	UF = 100 FQPA SF = 1×
Dermal exposure	N/A—Not required because of minimal dermal absorption		
Cancer	Inadequate information to assess carcinogenic potential		

[a] UF/SF refers to total of uncertainty and/or safety factors for dietary assessments. MOE refers to desired margin of exposure for occupational or residential assessments.

Appendix III Label Amendments for the Product Containing Streptomycin

The label amendments presented below do not include all label requirements for individual end-use products, such as first aid statements, disposal statements, precautionary statements and supplementary protective equipment. Additional information on the label of the currently registered product should not be removed unless it contradicts the above label statements.

A submission to request label revisions will be required within 90 days of finalization of the re-evaluation decision.

The label of the end-use product in Canada must be amended to include the following statements to further protect workers and the environment.

I) The following statements must be included in the **DIRECTIONS FOR USE** section.

> This product contains the antibiotic streptomycin. To reduce the development of drug-resistant bacteria and maintain the effectiveness of streptomycin and other antibacterial products in humans, this product should be used only when it is absolutely necessary to treat or prevent fire blight infection.

II) The following statements must be included in the **ENVIRONMENTAL HAZARDS** section.

> This product is toxic to algae. DO NOT apply this product directly to freshwater habitats (such as lakes, rivers, sloughs, ponds, prairie potholes, creeks, marshes, streams, reservoirs and wetlands), estuarine/marine habitats. DO NOT contaminate irrigation or drinking water supplies or aquatic habitats by cleaning of equipment or disposal of wastes.